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(21) International Application Number: PCT/US98/23233 (22) International Filing Date: 10 November 1998 (10.11.98) (30) Priority Data: <table border="0"> <tr> <td>60/065,689</td> <td>18 November 1997 (18.11.97)</td> <td>US</td> </tr> <tr> <td>60/071,297</td> <td>16 January 1998 (16.01.98)</td> <td>US</td> </tr> <tr> <td>60/073,662</td> <td>4 February 1998 (04.02.98)</td> <td>US</td> </tr> <tr> <td>60/075,247</td> <td>19 February 1998 (19.02.98)</td> <td>US</td> </tr> <tr> <td>60/077,672</td> <td>12 March 1998 (12.03.98)</td> <td>US</td> </tr> </table> (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BATTIS, Donald, H. [US/US]; 4303 Old Colony, Kalamazoo, MI 49008 (US). ULRICH, Roger, G. [US/US]; Apartment 333, 1350 S. White Oak Drive, Waukegan, IL 60085 (US). (74) Agent: STEIN, Bruce; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).		60/065,689	18 November 1997 (18.11.97)	US	60/071,297	16 January 1998 (16.01.98)	US	60/073,662	4 February 1998 (04.02.98)	US	60/075,247	19 February 1998 (19.02.98)	US	60/077,672	12 March 1998 (12.03.98)	US	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: USE OF OXAZOLIDINONE DERIVATIVES FOR TREATING PSORIASIS, ARTHRITIS AND REDUCING THE TOXICITY OF CANCER CHEMOTHERAPY (57) Abstract <p>The present invention is a method of treating a person who has psoriasis or arthritis or reducing the toxicity of cancer chemotherapy which comprises administering to the patient an anti-psoriasis effective amount of an oxazolidinone, preferably (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.</p>																	

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USE OF OXAZOLIDINONE DERIVATIVES FOR TREATING PSORIASIS, ARTHRITIS AND
REDUCING THE TOXICITY OF CANCER CHEMOTHERAPY

1. Field of the Invention

5 The present invention is the use of known oxazolidinones to treat psoriasis, arthritis and to reduce the toxicity of cancer chemotherapy.

2. Description of the Related Art

US Patents 5,164,510, 5,231,188, 5,565,571, 5,652,238 and 5,688,792 all
disclose various oxazolidinone antibiotics which are well known to those skilled in
10 the art.

Psoriasis is a well known condition, a proliferative disease of the skin of unknown etiology. It is not known, or believed, to have a microbiologic cause.

Problems experienced by those suffering with psoriasis include intense itching and discomfort, unsightly skin blemishes and chronic scratching resulting in
15 skin infections.

At present there are no cures, only methods of dealing with the clinical symptoms experienced by the patients. These methods of treatment include avoiding drying of the skin and irritation of skin, use of topical steroid cremes and ointments, use of crude coal tar (1-5% in an ointment base) applied topically,
20 ultraviolet light therapy, topical vitamin D (calcipotriol), oral methotrexate for severe cases (a drawback to this therapy is that methotrexate causes severe liver damage if not careful), use of etretinate (a synthetic retinoid) for severe cases (however a drawback to this therapy is that it is associated with severe deformities in fetuses if a female patient is pregnant).

25 There is no cure for psoriasis, but rather treatments which may induce a remission for a period of time. Since the pathogenesis of psoriasis is unknown, the reason why the various treatments do not fully succeed is not known but it is likely that present treatments are not treating the root cause of psoriasis.

While there are number of pharmaceutical agents available for treating
30 psoriasis, none treat the condition/disease as well as psoriasis sufferers or physicians would like.

Arthritis, inflammation of the joint tissues, has numerous causes including bacterial infection (septic arthritis), degeneration of articular surfaces (osteoarthritis), immunologic reaction against joint tissues (rheumatoid
35 arthritis), crystal induced arthritis (gouty arthritis, pseudogout) and other miscellaneous causes (Reiter's syndrome, etc). One common thread in

all of these is inflammation in and around the joint. Present day therapeutics for arthritis are not curative unless the arthritis is infectious and the underlying pathogen is eliminated by an antibiotic. For other types of arthritis medications can reduce pain or inflammation but do not cure the disease. The OXAZOLIDINONEs can be used to treat the inflammation and pain caused by arthritis, including those types of arthritis which are not caused by infection. This is important since all of the medications presently available to treat arthritis have severe side effects. Steroidal medications (glucocorticoids like prednisone and cortisol) give stomach ulcers, cataracts, reduced resistance to infection, weight gain and thinning of skin. Non-steroidal anti-inflammatory drugs (NSAIDS such as indomethacin or ibuprofen among others) can cause stomach ulcers, reduced kidney function and bone marrow effects. Chemotherapeutic agents (like methotrexate) can have severe adverse effects on bone marrow and liver function. The OXAZOLIDINONEs provide the opportunity for relief of symptoms of inflammation for patients intolerant of other types of arthritis medications.

Patients who have cancer and need to undergo anti-cancer chemotherapy have the problem that the dose limiting factor in their treatment is the suppression of bone marrow. The present invention prevents and reduces the amount of suppression of bone marrow and injury to intestinal crypt cells (the cells that produce new intestinal cells). By preventing damage to the hematopoietic cells in general and the bone marrow cells in particular, physicians can prevent or reduce the toxicity of the chemotherapeutic agents and therefore can treat cancer patients longer and/or with higher doses and with reduced risks of complications. All this means a more successful outcome for the patient.

At present there is no product on the market that prevents damage to hematopoietic and/or intestinal cells from exposure to anti-cancer chemotherapeutic agents. There are products which are given after anti-cancer chemotherapy to try and help the patient recover, but this is not the same as the preventive method of the present invention. These agents include bone marrow colony stimulating factors such as GM-CSF. There are protective agents known, but not in clinical use, for dealing with radiation therapy such as glutathione derivatives, but these do not prevent the problems associated with anti-cancer chemotherapy.

SUMMARY OF INVENTION

Disclosed is a method of treating a person who has psoriasis which comprises administering to the patient an anti-psoriasis effective amount of an oxazolidinone

selected from the group consisting of:

(S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

[4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,

(S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and pharmaceutically acceptable salts thereof.

Also disclosed is a method of treating a person who has arthritis which comprises administering to the patient an anti-arthritis effective amount of an oxazolidinone selected from the group consisting of the six oxazolidinones set forth above.

Further disclosed is a method of reducing damage to hematopoietic cells and intestinal cells in a person being treated with one or more anti-cancer chemotherapeutic agents which comprises administering to the human an anti-cytotoxic effective amount of an oxazolidinone selected from the group consisting of the six oxazolidinones set forth above.

DETAILED DESCRIPTION OF THE INVENTION

The oxazolidinones of the present invention are known, see EXAMPLES 1 thru 6 (OXAZOLIDINONES) and pharmaceutically acceptable salts thereof.

Suitable pharmaceutical acceptable salts include the acid addition salts from the both inorganic and organic acids including hydrochloric, hydrobromic, sulfuric, phosphoric, sulfonic acids, methanesulfonic, gluconic, galacturonic, citric, oxalic and acetic.

It is preferred that the person being treated for psoriasis or arthritis or with cancer chemotherapy agents with OXAZOLIDINONES does not have a gram positive bacterial infection at the time of being treated.

In treating psoriasis, the OXAZOLIDINONES can either be used individually or in combination with each other or in combination with non-OXAZOLIDINONES.

In treating psoriasis, the OXAZOLIDINONES are administered orally, parenterally (IV), topically or rectally.

When administered orally, the OXAZOLIDINONEs can be administered in tablet, capsule or liquid (suspension, syrup or solution) dosage form. Regardless of the dosage form, an anti-psoriasis effective amount of the OXAZOLIDINONEs is from about 50 mg to about 1,200 mg/day. It is preferred that the

5 OXAZOLIDINONEs be given in two or more divided doses, more preferably in two divided doses.

When administered parenterally, the OXAZOLIDINONEs should be administered IV. The IV infusion should be adjusted such that the flow rate delivers an anti-psoriasis effective amount of from about 50 mg to about 1,200
10 mg/day. (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is virtually 100% bioavailable. Therefore, the patient will achieve approximately the same blood levels with the same dose regardless of whether it is given orally or parenterally.

When applied topically, the OXAZOLIDINONEs can be applied in many
15 different pharmaceutical dosage forms all well known to those skilled in the art. These include as a solution, cream, ointment, gel, lotion, suspension or emulsion, etc. Regardless of the topical pharmaceutical dosage form selected, the concentration of the OXAZOLIDINONEs should be from about 0.01% to about 10% (wt/wt). Regardless of the pharmaceutical dosage form, the topical formulation
20 should be applied one to four times daily.

When administered rectally, the OXAZOLIDINONEs should be administered as a suppository which delivers an anti-psoriasis effective amount of from about 50 mg to about 1,200 mg/day.

When administered systemically, whether orally, parenterally or rectally the
25 OXAZOLIDINONEs should be administered either continuously or in cyclic courses of 7-28 days every 1 to 12 months. When administered topically, the OXAZOLIDINONEs should be applied either daily for 7 to 28 days every 1 - 12 months.

In treating arthritis, the OXAZOLIDINONEs can either be used individually
30 or in combination with each other or in combination with non-OXAZOLIDINONEs.

In treating arthritis, the OXAZOLIDINONEs are administered orally, parenterally (IV), topically or rectally.

When administered orally, the OXAZOLIDINONEs can be administered in tablet, capsule or liquid (suspension, syrup or solution) dosage form. Regardless of
35 the dosage form, an anti-arthritis effective amount of the OXAZOLIDINONEs is from about 50 mg to about 1,200 mg/day. It is preferred that the

OXAZOLIDINONEs be given in two or more divided doses, more preferably in two divided doses.

When administered parenterally, the OXAZOLIDINONEs should be administered IV. The IV infusion should be adjusted such that the flow rate
5 delivers an anti-arthritis effective amount of from about 50 mg to about 1,200 mg/day. This can be done by a continuous infusion, or as divided doses given as short term infusions of 30-90 minutes, preferably twice a day.

When applied topically, the OXAZOLIDINONEs can be applied in many different pharmaceutical dosage forms all well known to those skilled in the art.
10 These include a solution, cream, ointment, gel, lotion, suspension or emulsion. Regardless of the pharmaceutical dosage form selected, the concentration of the OXAZOLIDINONEs should be from about 0.01% to about 10% (wt/wt). Regardless of the pharmaceutical dosage form, the topical formulation should be applied one to four times daily.

15 When administered rectally, the OXAZOLIDINONEs should be administered as a suppository which delivers an anti-arthritis effective amount of from about 50 mg to about 1,200 mg/day.

When administered systemically, whether orally, parenterally or rectally the OXAZOLIDINONEs should be administered either continuously or in cyclic courses
20 of 7-28 days every 1 to 12 months. When administered topically, the OXAZOLIDINONEs should be applied either daily for 7 to 28 days every 1 - 12 months.

The exact dosage and frequency of administration depends on the particular OXAZOLIDINONE used, the severity of the condition being treated, the age, weight,
25 general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the OXAZOLIDINONE in the patient's blood and/or the patient's response to the particular condition being treated.

30 Individuals who have cancer and are treated with anti-cancer chemotherapeutic agents experience damage to their hematopoietic and intestinal cells. There are three types of hematopoietic cells. These are bone marrow cells, spleen cells and liver cells. It is preferred that the hematopoietic cells be bone marrow cells. The present method also prevents/reduces damage to intestinal crypt
35 cells. These are the cells located in the intestinal area that produce new intestinal cells.

By preventing damage to the hematopoietic cells in general and the bone marrow cells in particular, physicians can prevent or reduce the toxicity of the chemotherapeutic agents and therefore can treat cancer patients longer and/or with higher doses and with reduced risks of complications. All this means a more
5 successful outcome for the patient.

In preventing/reducing the damage to hematopoietic cells and intestinal cells from exposure to anti-cancer chemotherapeutic agents, the OXAZOLIDINONEs can either be used individually or in combination with each other or in combination with non-OXAZOLIDINONEs.

10 In some cases the present method will prevent the damage from occurring and in other cases it will reduce the damage that would have occurred if the patient had not been treated with the OXAZOLIDINONEs. As used here, reduction is a form of prevention; prevention is the ultimate reduction.

The present method is practiced by preferably pre-treating the patient for
15 about 2 to about 20 days prior to the patient being treated with an anti-cancer chemotherapeutic agent. It is more preferable that the pretreatment be from about 5 to about 7 days prior to the patient being treated with an anti-cancer chemotherapeutic agent. Alternatively, the OXAZOLIDINONEs can be administered concurrently with the anti-cancer chemotherapeutic agent.

20 Anti-cancer chemotherapeutic agents which are included in the method of reducing damage according to the present invention are selected from four different types of chemotherapeutic agents. These are:

(1) DNA-interactive agents (including alkylating agents, DNA strand-breakage agents, DNA topoisomerase I and II inhibitors, DNA minor groove binders)
25 such as chlorambucil, cyclophosphamide, thiotepa, busulfan, carmustine, cisplatin, carboplatin, mitomycin, procarbazine, bleomycin, amsacrine, daunorubicin, doxorubicin, etoposide, plicamycin, camptothecin and irinotecan;

(2) antimetabolites (including folate antagonists, purine antagonists, pyrimidine antagonists) such as methotrexate, mercaptopurine, eloxuridine and
30 fluorouracil;

(3) tubulin-interactive agents such as vinblastine, vincristine and paclitaxel;

(4) hormonal agents such as dienestrol, diethylstilbestrol, estradiol, tamoxifen and fluoxymesterone.

It is preferred that the anti-cancer chemotherapeutic agent be selected from
35 the group consisting of chlorambucil, cyclophosphamide, thiotepa, busulfan, carmustine, cisplatin, carboplatin, mitomycin, procarbazine, bleomycin, amsacrine,

daunorubicin, doxorubicin, etoposide, plicamycin, camptothecin, ironotecan, methotrexate, mercaptopurine, eloxuridine, fluorouracil, vinblastin, vincristine, paclitaxel, dienestrol, diethylstilbestrol, estradiol, tamoxifen and fluoxymesterone. It is more preferred that the anti-cancer chemotherapeutic agent be selected from the group consisting of etoposide, irinotecan, fluorouracil and paclitaxel.

In preventing/reducing the damage to hematopoietic cells and intestinal cells from exposure to anti-cancer chemotherapeutic agents, the OXAZOLIDINONES are administered orally, parenterally (IV) or rectally. It is preferred that the OXAZOLIDINONES be administered orally or by IV, more preferably orally.

When administered orally, the OXAZOLIDINONES can be administered in solid (tablet or capsule) or liquid (suspension, syrup or solution) dosage form. Regardless of the dosage form, a cytostatic or an anti-cytotoxic effective amount of the OXAZOLIDINONES is from about 50 mg to about 1,200 mg/day. It is preferred that the OXAZOLIDINONES be given in two or more divided doses, more preferably in two divided doses.

When administered parenterally, the OXAZOLIDINONES should be administered IV. The IV infusion should be adjusted such that the flow rate delivers an anti-cytotoxic effective amount of from about 50 mg to about 1,200 mg/day. This can be done by a continuous infusion, or as divided doses given as short term infusions of 30-90 minutes, preferably twice a day.

When administered rectally, the OXAZOLIDINONES should be administered as a suppository which delivers an anti-cytotoxic effective amount of from about 50 mg to about 1,200 mg/day.

When administered systemically, whether orally, parenterally or rectally the OXAZOLIDINONES should be administered either continuously or in cyclic courses of 7-28 days every 1 to 12 months.

The exact dosage and frequency of administration depends on the particular OXAZOLIDINONE used, the particular anti-cancer chemotherapeutic agent used, the dose of the anti-cancer chemotherapeutic agent, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the OXAZOLIDINONE in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout

this entire document including both the specification and the claims.

DEFINITIONS

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

When the % active ingredient of a pharmaceutical formulation is set forth, it is the ratio of the active ingredient of the entire pharmaceutical formulation and is expressed as weight/weight (wt/wt).

Alcohol refers to ethyl alcohol.

IV refers to parenteral administration by the intravenous route.

OXAZOLIDINONES refers to the compounds of EXAMPLES 1 thru 6.

Anti-cytotoxic refers to reducing and/or preventing normal cell death.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,652,238, EXAMPLE 1.

EXAMPLE 2 (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,688,792, EXAMPLE 5.

EXAMPLE 3 [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-

oxo-5-oxazolidinyl)methyl]acetamide S-oxide (International Publication No. WO 97/09328, 4.50 g) and platinum oxide (697 mg) in methanol (164 ml) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). The appropriate fractions (those fractions with an $R_f = 0.44$ by TLC; methanol/chloroform, 10/90) are pooled and concentrated to give the title compound, mp 203 - 204°.

10 **EXAMPLE 4** N-((5S)-3-(3-Fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide

N-((5S)-3-(3-Fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide is known, see International Publication WO97/27188 (Example 4).

15 1-*t*-Butoxycarbonyl-3-oxopiperazine (21.6 g) is dissolved in dry DMF (500 ml) and potassium *t*-butoxide (24.2 g) is added. The mixture is stirred at 20-25° for 30 minutes, then 1-(4-methylphenylsulfonyloxy)-2-fluoroethane (*J. Med. Chem.*, 23(9), 985-90 (1980), 25.9 g) is added and stirring continued at the same temperature for 24 hours. The solvent is removed and the residue partitioned between ethyl acetate and water. The organic phase is washed with water and concentrated. The residue is dissolved in isopropanol and diluted with iso-hexane forming a precipitate which is removed by filtration. The mixture is chromatographed (silica; eluting with a gradient increasing in polarity from 0 to 50% isopropanol in iso-hexane) to give 1-*t*-butoxycarbonyl-4-(2-fluoroethyl)-3-oxopiperazine.

25 1-*t*-Butoxycarbonyl-4-(2-fluoroethyl)-3-oxopiperazine (6.65 g) is dissolved in dichloromethane (500 ml), cooled in an ice-bath and trifluoroacetic acid (150 ml) added. The mixture is stirred at the same temperature for 2 hours. The solvent is removed to give a crude product which is dissolved in the minimum volume of ethyl acetate. Slow addition of ether causes precipitation of 1-(2-fluoroethyl)-2-oxopiperazine as the mono trifluoroacetic acid salt.

30 1-(2-Fluoroethyl)-2-oxopiperazine trifluoroacetate (6.1 g) is dissolved in acetonitrile (100 ml). N,N-Diisopropylethylamine (13 ml) is added to the mixture, followed by 3,4-difluoronitrobenzene (3.39 g) and the mixture heated to reflux for 18 hours. The solvent is removed and the residue chromatographed (silica; eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane) to give 3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)nitrobenzene.

3-Fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)nitrobenzene (4.35 g) is dissolved in a mixture of ethyl acetate (250 ml) and DMF (5 ml), and the solution flushed with argon. Palladium (10% on carbon, 200 mg) is added and the mixture hydrogenated under ambient pressure. After gas uptake had ceased, the mixture is
5 filtered through celite and solvent removed. The residue is taken up in ethyl acetate, washed twice with water, dried over magnesium sulfate and the solvent is removed to give 5-amino-2-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]fluorobenzene which is used without further purification.

5-Amino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene (2.6 g) is
10 dissolved in dry dichloromethane (50 ml) under argon. Pyridine (1.03 ml) is added, and the mixture cooled to -20° . Benzyl chloroformate (1.6 ml) is added and the mixture stirred for 10 minutes at -20° , before allowing the temperature to rise to $20-25^{\circ}$ over 1.5 hours. The solvents are removed and the residue is dissolved in
15 dichloromethane and washed with sodium bicarbonate solution. After drying over magnesium sulfate and removal of the solvent, the residue is chromatographed (silica, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane) to give 5-benzyloxycarbonylamino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene.

A solution of lithium *t*-butoxide is prepared by addition of *n*-butyllithium (1.6
20 M in hexane, 2.9 ml) to a stirred solution of *t*-butanol (0.43 g) in anhydrous THF (10 ml) at -10° under argon. After cooling to -70° , a solution of 5-benzyloxycarbonylamino-2-(4-[2-fluoroethyl]-3-oxopiperazin-1-yl)fluorobenzene (1.5 g) in dry THF (15 ml) is added. After 10 minutes, (R)-glycidylbutyrate (0.67 g) in dry THF (15 ml) is added to the resulting mixture, and stirring continued at -70° for 15
25 minutes, before allowing the temperature to rise to $20-25^{\circ}$ over 16 hours. Methanol (10 ml) is added, followed by saturated sodium bicarbonate solution (20 ml) and water (10 ml). The organic phase is separated and extracted into ethyl acetate (3 x 25 ml), washed with saline and dried over magnesium sulfate. The solvent is removed and the residue purified by chromatography (silica; eluting with a gradient
30 increasing in polarity from 0 to 3% methanol in dichloromethane) to give (5R)-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-hydroxymethyloxazolidin-2-one.

(5R)-3-(3-Fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-hydroxymethyloxazolidin-2-one (0.8 g) is dissolved in pyridine (15 ml) and the
35 mixture cooled to 0° . Triethylamine (0.38 ml) and methanesulfonyl chloride (0.19 ml) are added to the mixture, and stirring continued at $20-25^{\circ}$ for 2 hours. The

solvent is removed and the residue dissolved in dichloromethane, washed with water, saline, dried over magnesium sulfate and concentrated. The resulting residue is triturated with ether to give (5R)-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)-5-(methanesulfonyloxymethyl)oxazolidin-2-one (0.76 g) which is used without further purification.

(5R)-3-(3-Fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]-5-(methanesulfonyloxymethyl)oxazolidin-2-one (719 mg) is dissolved in dry DMF (15 ml) and sodium azide (647 mg) is added to the mixture. The mixture is heated at 80° for 6 hrs and then concentrated to dryness. The resulting residue is dissolved in ethyl acetate, washed twice with water, and dried over magnesium sulfate. Removal of the solvent gives (5R)-5-azidomethyl-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)oxazolidin-2-one (413 mg) which is used without further purification.

(5R)-5-Azidomethyl-3-(3-fluoro-4-[4-(2-fluoroethyl)-3-oxopiperazin-1-yl]phenyl)oxazolidin-2-one (360 mg) is dissolved in dry DMF (20 ml) and the mixture purged with argon. Palladium (10% on carbon, 72 mg) is added, followed by acetic anhydride (0.17 ml) and the mixture stirred at 20-25° under hydrogen confined in a balloon for 3 hr. The mixture is filtered through celite, concentrated to dryness and partitioned between ethyl acetate and water. The organic extract is washed with saline, dried over magnesium sulfate and concentrated. The residue is chromatographed (silica gel; eluting with a gradient increasing in polarity from 0 to 2.5% methanol/dichloromethane). The appropriate fractions are pooled and concentrated to give the title compound.

EXAMPLE 5 (S)-N-[[3-[5-(3-Pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(S)-N-[[3-[5-(3-Pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide is known, see US Patent 5,698,574 (Example 124).

EXAMPLE 6 (S)-N-[[3-[5-(4-Pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride

(S)-N-[[3-[5-(4-Pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride is prepared following the general procedure of US Patent 5,627,181 EXAMPLES 36 and 52 and making non-critical variations but using a 4-pyridinyl adduct.

EXAMPLE A 47 Year Old White Male - Psoriasis

A 47 year old white male had a history of psoriasis since age 32. He had chronic psoriatic lesions of both elbows, groin, left leg, right leg, and lower back. The lesions were treated in the past with coal tar and topical steroids but not UV

light. He was allergic to the excipients in the steroidal topical preparations.

He was treated with 625 mg of (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide IV twice daily for five days and then with 625 mg of the same pharmaceutical orally twice daily for nine days. Hence, the patient
5 was given 625 mg of (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide twice daily for fourteen days and noticed an immediate improvement in his psoriasis as soon as he started taking the medication. He had a complete clearing of the psoriasis from the time he took the medication until three months later when it gradually began to return. After six months it had
10 returned to the pretreatment state. During the time he took the oxazolidinone he did not use any other psoriasis treatment.

EXAMPLE B 50 Year Old White Male - Arthritis

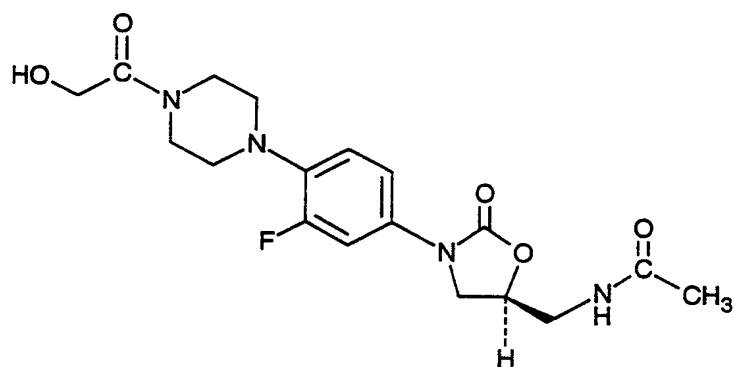
A 50 year old white male (Subject No 1912) who had a history of chronic obstructive pulmonary disease (i.e. he was a smoker), hypertension, coronary artery
15 disease and arthritis of the "legs, arms and shoulders" for which he took non steroidal antiinflammatory agents including aspirin, developed community acquired pneumonia with *Streptococcus pneumoniae* as evidenced by an abnormal chest X-ray. He is treated with 625 mg of (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide twice daily intravenously for 3 days followed by 8
20 days of oral (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide at the same dose.

At long term follow up the patient stated that his arthritis was gone and he was taking no medications.

CHART A

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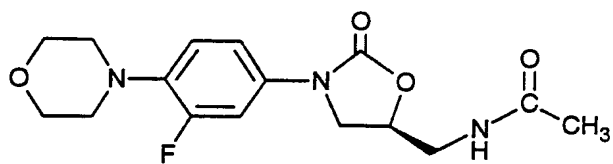
EXAMPLE 1



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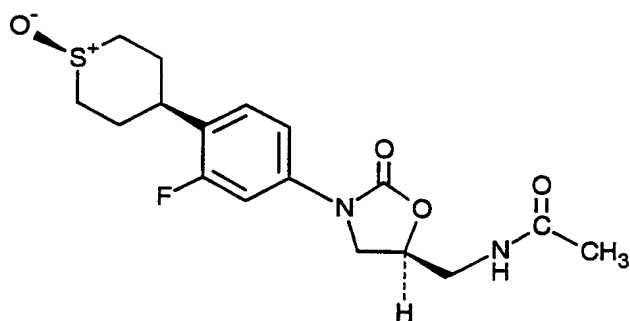
EXAMPLE 2



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EXAMPLE 3



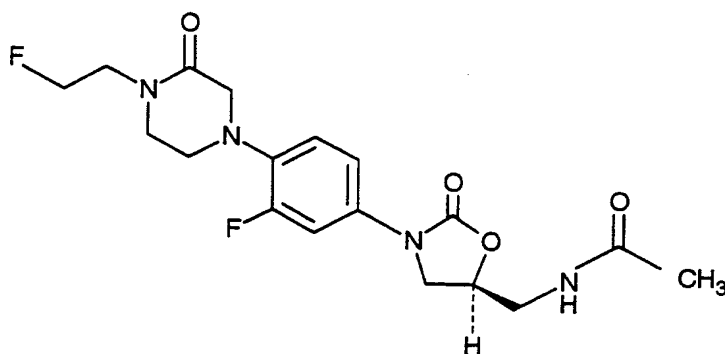
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CHART A - continued

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EXAMPLE 4

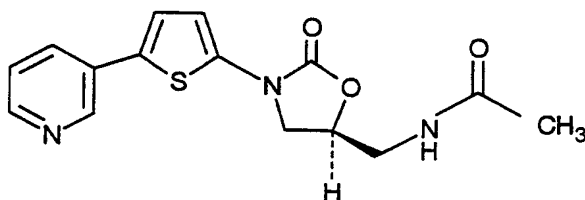
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EXAMPLE 5

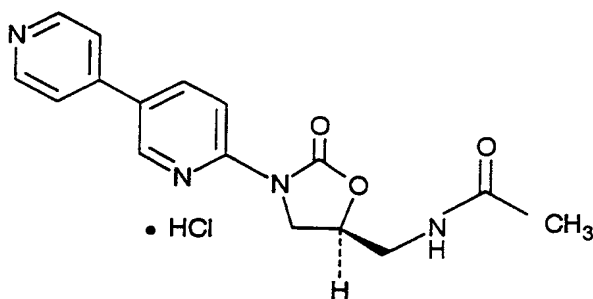
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EXAMPLE 6

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CLAIMS

1. Use of an oxazolidinone selected from:
 (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
5 (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
 [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
 N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,
10 (S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide
 and
 (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and
 pharmaceutically acceptable salts thereof for the manufacture of a medicament for
15 use in treating psoriasis where the human to be treated does not have a gram
 positive bacterial infection.
2. Use of an oxazolidinone according to claim 1 where the medicament is administered orally.
- 20 3. Use of an oxazolidinone according to claim 2 where the daily dose of the oxazolidinone is from about 50 to about 1,200 mg/day.
- 25 4. Use of an oxazolidinone according to claim 1 where the medicament is administered topically as a solution, cream, ointment, gel, lotion, suspension or emulsion.
- 30 5. Use of an oxazolidinone according to claim 1 where the amount to be administered topically is from about 0.01% to about 10%.
6. Use of an oxazolidinone according to claim 1 where the medicament is administered IV.
- 35 7. A method of treating a person who has psoriasis according to claim 7 where the amount to be administered IV is from about 50 to about 1,200 mg/day.

8. Use of an oxazolidinone according to claim 1 where the oxazolidinone is (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.
9. Use of an oxazolidinone selected from:
- 5 (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
[4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,
10 N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,
(S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide
and
15 (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and
pharmaceutically acceptable salts thereof for the manufacture of a medicament for
use in treating arthritis where the human to be treated does not have a gram
positive bacterial infection.
- 20 10. Use of an oxazolidinone according to claim 9 where the medicament is
administered orally.
11. Use of an oxazolidinone according to claim 10 where the daily dose of the
oxazolidinone is from about 50 to about 1,200 mg/day.
- 25 12. Use of an oxazolidinone according to claim 9 where the medicament is
administered topically as a solution, cream, ointment, gel, lotion, suspension or
emulsion.
- 30 13. Use of an oxazolidinone according to claim 12 where the amount to be
administered topically is from about 0.01% to about 10%.
14. Use of an oxazolidinone according to claim 9 where the medicament is
administered IV.
- 35 15. Use of an oxazolidinone according to claim 14 where the amount to be

administered IV is from about 50 to about 1,200 mg/day.

16. Use of an oxazolidinone according to claim 9 where the oxazolidinone is (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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17. Use of an oxazolidinone selected from:

(S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

10

[4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide,

15

(S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

(S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide and pharmaceutically acceptable salts thereof for the manufacture of a medicament for reducing damage to hematopoietic cells and intestinal cells in a person being treated with one or more anti-cancer chemotherapeutic agents where the human to be treated does not have a gram positive bacterial infection.

20

18. Use of an oxazolidinone according to claim 17 where the hematopoietic cell is a bone marrow cell.

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19. Use of an oxazolidinone according to claim 17 where the hematopoietic cell is a spleen cell.

20. Use of an oxazolidinone according to claim 17 where the medicament is administered for a period of from about 2 to about 20 days prior to treatment with an anti-cancer chemotherapeutic agent.

30

21. Use of an oxazolidinone according to claim 20 where the medicament is administered for a period of from about 5 to about 7 days prior to treatment with an anti-cancer chemotherapeutic agent.

35

22. Use of an oxazolidinone according to claim 17 where the medicament is administered concurrently with the anti-cancer chemotherapeutic agent.
23. Use of an oxazolidinone according to claim 17 where the anti-cancer
5 chemotherapeutic agent is selected from the group consisting of:
chlorambucil, cyclophosphamide, thiotepa, busulfam, carmustine, cisplatin, carboplatin, mitomycin, procarbazine, bleomycin, amsacrine, daunorubicin, doxorubicin, etoposide, plicamycin, camptothecin, irinotecan, methotrexate, mercaptopurine, eloxuridine, fluorouracil, vinblastin, vincristine, paclitaxel,
10 dienestrol, diethylstilbestrol, estradiol, tamoxifen and fluoxymesterone.
24. Use of an oxazolidinone according to claim 23 where the anti-cancer chemotherapeutic agent is selected from the group consisting of etoposide, irinotecan, fluorouracil and paclitaxel.
15
25. Use of an oxazolidinone according to claim 17 where the medicament is administered from about 50 mg to about 1,200 mg/day.
26. Use of an oxazolidinone according to claim 17 where the oxazolidinone is (S)-N-
20 [[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 98/23233

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 23384 A (THE UPJOHN COMPANY) 25 November 1993 see claims 1-13 ---	1-26
A,P	US 5 688 792 A (M. R. BARBACHYN ET AL) 18 November 1997 cited in the application see the whole document ---	1-26
A	WO 95 14684 A (THE UPJOHN COMPANY) 1 June 1995 see the whole document & US 5 652 238 A cited in the application --- -/--	1-26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 March 1999

Date of mailing of the international search report

23/03/1999

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Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

Int nal Application No

PCT/US 98/23233

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see the whole document & US 5 565 571 A cited in the application -----</p>	1-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 23233

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 7
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-16
2. Claims: 17-26

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-16

Use of oxazolidinone derivatives to treat psoriasis or arthritis, both of which are inflammatory diseases

2. Claims: 17-26

Use of oxazolidinone derivatives to reduce damage to hematopoietic and intestinal cells in cancer chemotherapy patients

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23233

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323384 A	25-11-1993	AU 668733 B	16-05-1996
		AU 4287793 A	13-12-1993
		CA 2133079 A	25-11-1993
		CN 1079964 A	29-12-1993
		CZ 9402505 A	16-08-1995
		EP 0640077 A	01-03-1995
		FI 945246 A	08-11-1994
		HU 72296 A	29-04-1996
		HU 9500659 A	28-11-1995
		IL 105555 A	15-07-1998
		JP 7506829 T	27-07-1995
		MX 9302665 A	01-11-1993
		NO 944237 A	04-01-1995
		PL 174909 B	30-10-1998
		PL 174850 B	30-09-1998
		SK 133794 A	07-06-1995
		US 5547950 A	20-08-1996
		US 5700799 A	23-12-1997
		ZA 9302855 A	24-10-1994
US 5688792 A	18-11-1997	AU 687866 B	05-03-1998
		AU 7557094 A	27-03-1995
		EP 0717738 A	26-06-1996
		JP 9502436 T	11-03-1997
		NZ 271805 A	26-02-1998
WO 9514684 A	01-06-1995	AU 698699 B	05-11-1998
		AU 8010394 A	13-06-1995
		CA 2174107 A	01-06-1995
		CN 1135752 A	13-11-1996
		EP 0730591 A	11-09-1996
		JP 9505582 T	03-06-1997
		NZ 274966 A	26-01-1998
		US 5652238 A	29-07-1997
		ZA 9407885 A	09-04-1996
WO 9309103 A	13-05-1993	AT 146783 T	15-01-1997
		AU 667198 B	14-03-1996
		AU 2689892 A	07-06-1993
		CA 2119556 A	13-05-1993
		DE 69216251 D	06-02-1997
		DE 69216251 T	15-05-1997
		DK 610265 T	09-06-1997
		EP 0610265 A	17-08-1994
		GR 3022340 T	30-04-1997
		JP 7500603 T	19-01-1995
		US 5565571 A	15-10-1996
		US 5801246 A	01-09-1998
		US 5654428 A	05-08-1997
		US 5756732 A	26-05-1998
		US 5654435 A	05-08-1997